TOBACCO INDUSTRY RESEARCH COMMITTEE
350 FIFTH AVENUE NEW YORK 1, N. Y.

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Application For Research Grant

Date: September 30, 1955

1. Name of Investigator: William E. Smith, M.D.

2. Title:

3. Institution & Address: 170 Glenwood Road, Englewood, New Jersey

4. Project or Subject: Experiments pertaining to lung tumors.

1. Exploration of specificity of a rapid test for carcinogenicity of chemicals.

2. Search for a virus in pulmonary adenomas of mice.

3. Investigation of dietary deficiency of choline in relation to lung tumors.

5. Detailed Plan of Procedure (Use reverse side if additional space is needed).

1. Enumeration of sebaceous glands and observations upon hair loss within ten days after application of test materials to mouse skin have provided a rapid means for predicting the relative carcinogenic potencies of derivatives of petroleum, coal tar and cigarette smoke, as indicated in attached material (Smith, W.E.; Sebaceous gland activity as a measure of the relative carcinogenicity of certain oils and tars. Bull. N.Y. Acad. Med., in press).

A purpose of the present project is to explore the specificity of these early changes through study of pure chemicals of varying carcinogenicity and structurally related but non-carcinogenic compounds. It is also intended to apply this technique for further study of derivatives of cigarette smoke.

As the originator of this technique, I have been offered an appointment as a visiting professor in the University of Paris, to work in the laboratory of Professor R. Truhaut at the Faculte' de Pharmacie, where studies of the potential carcinogenicity of cigarette smoke are being conducted under the auspices of the Institut National d'Hygiene de France. Supplies of pure chemicals of varying carcinogenicity have been offered by Professor A. Lacassagne, Director of the Institut du Radium, in Paris, which possesses a unique collection of such compounds.

Signature: /s/ William E. Smith, M.D.

2. Use of the tissue transplant technique for ascertaining carcinogenicity of materials upon lung tissue is commented upon in attached articles (Smith, W.E.: The tissue transplant technique as a means of testing materials for carcinogenic action, Cancer Research 1949, 9, 712-723; Lung cancer with special reference to experimental aspects, Arch. Indust. Hyg. & Occup. Med. 1952, 5, 209-217;

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Evaluation of claims for occupational factors in cancer of the lung, Acta Union Internat. contre le Cancer, 1953, 9, 476-484).

Cancers of the nasal sinuses and lung have appeared to be an occupational risk among employees of a nickel refinery. By means of the tissue transplant technique, I have in unpublished experiments induced transplantable adenocarcinomas by intramuscular implantation of nickel powder together with fetal lung tissue from C strain mice. I now am carrying one of these tumors in the third generation of new hosts. I wish to learn whether this tumor carries a virus capable of inducing similar growths. I propose to test for the presence of such an agent by exposing pulmonary tissue from mouse embryos of the A strain to be extracts of this tumor that was induced from pulmonary tissue from the C strain. The exposed pulmonary tissue will be transplanted into A strain hosts in an endeavor to avoid tumors from the growth of any intact C strain cells that may inadvertently be present in the extracts.

3. Clinical and experimental studies have indicated that several types of tumors may result from dietary deficiencies. Primary carcinomas of the lungs have been reported in 38% of rats fed a diet deficient in choline (Copeland and Salmon, Amer. Journ. Path. 1946, 22, 1059-1079). No lung tumors were found in control animals fed a diet supplemented with choline.

If these claims can be corroborated, they would open an interesting field of experimentation upon otiology and possibly treatment of lung tumors. It is therefore intended:

a) to repeat the feeding experiment of Copeland and Salmon, using a group of 100 rats (50 fed a diet deficient in choline, 50 fed the same diet but supplemented with choline).

b) to conduct a similar experiment with 100 mice of the A strain with special reference to any alteration in the frequency of pulmonary adenomas among them.

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6. Budget Plan:

Salaries	Principal investigator	$10,000
	Histologist-technician	3,000
	Animal caretaker	500 part salary
Expendable Supplies	(animals, chemicals)	1,200
Permanent Equipment		500
Overhead	(10%)	1,520
Other	(travel, investigator & family, one way)	1,200
Total per year		17,920

1. Name of Investigator: William E. Smith, M.D.

7. Anticipated Duration of Work:

Two years beginning March 1, 1956

8. Facilities and Staff Available:

Laboratory facilities, maintenance of animals and histological services will be provided by the Faculte' de Pharmacie, Universite' de Paris, Av. de l'Observatoire, Paris 6°, France.

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9. Additional Requirements:

None

5. Detailed Plan of Procedure (Use reverse side if additional space is needed)

10. Additional Information (Including relation of work to other projects and other sources of supply):

The Institut National d'Hygiene de France has appointed Professors Lacassagne, Oberling and Truhaut to conduct, in their respective laboratories, studies upon the potential carcinogenicity of smoke from various types of tobacco and to identify any carcinogens that may be present. Professor Truhaut has invited me to work in his laboratory in order to apply my rapid test for carcinogens to some of the materials developed in the course of this program.

Extensive studies on molecular structure in relation to carcinogenicity have been conducted for many years at the Institut du Radium in Paris. As a result, this institution possesses a unique collection of carcinogens and related compounds. The director, Professor Lacassagne, and his associate, Professor Buu Hoi, have consented to supply appropriate samples and advice for intelligent selection of compounds to explore the specificity of the rapid test for carcinogenicity described in this application. The applicant speaks French.

Signature s/ William E. Smith, M.D.
Director of Projects

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